REMARKS

New claims 116-121 are added above. New claim 116 recites that the tumor is a mesothelioma, i.e., one of the alternatives recited in claim 23. Claims 117-120 each recite that the patient is one who has had a tumor removed. This is one of two alternative recitations in independent claim 22 from which new claims 116-120 ultimately depend. New claim 121 recites that the previously recited *Listeria monocytogenes* bacterium is attenuated. This is supported in the specification at paragraphs 59, 61, and 68. These new claims are fully supported and do not add new matter to the application.

Claims 22-38, 111 and 113-115 were previously pending in the present application. Claim 25 was withdrawn from consideration. Upon the addition of the new claims, the currently examined claim set will include claims 22-24, 26-38, 111 and 113-121. No amendment or cancellation of claims dedicates to the public any of the subject matter of the claims as previously presented.

The Rejection of Claims 22-38, 11, 113-115 Under 35 U.S.C. §112, First Paragraph

All previously examined claims stand rejected under 35 U.S.C. 112, first paragraph, for allegedly not being enabled. More specifically, the Patent and Trademark Office (PTO) has alleged, "Applicants have not demonstrated with a preponderance of corroborating or convincing evidence that any form of DNA encoding the mesothelin protein comprising any one or more of the inventive peptides when administered to a human patient would in fact provide 'efficacy' insofar as increasing survival or improving life expectancy by inducing an MHC-specific and CTL-specific response to an epitope of the mesothelin protein, regardless of what form the DNA is administered, e.g., naked vector, adenoviral vector composition, an expressed recombinant protein on a *Lysteria* [*sic*] *monocytogenes* bacterium, etc." Office Action at page 3. Applicants respectfully traverse this rejection.

The enablement requirement of 35 U.S.C. § 112, first paragraph, requires that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue experimentation. *In re Wands*, 858 F. 2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988). See also MPEP 2164.01. As articulated in the MPEP, the "scope of enablement must only bear a

'reasonable correlation' to the scope of the claims." MPEP 2164.08. Further, the Patent and Trademark Office's determination of enablement must be based on the totality of the evidence that Applicants have presented. MPEP 2164.05.

In applicants' April 30, 2007 response to the Patent and Trademark Office's initial rejection of all claims for an alleged lack of enablement, Applicants (a) highlighted *in vivo* experiments described in the specification which support enablement of the claimed invention, and (b) provided evidence of additional experiments which further support enablement of the claimed invention in the form of a Declaration by inventor Elizabeth Jaffee, M.D. and additional publications (Exhibits 2-6 of the response). A summary of the experimental data presented in the specification and the previously submitted exhibits is provided in Exhibit A.[1]

In maintaining the enablement rejection despite the submission of such experimental evidence, the PTO appears to consider each piece of experimental evidence presented by applicants in the Response filed April 30, 2007 to be of little or no relevance to the claimed invention. Contrary to the PTO's position, however, one skilled in the art would consider the evidence already presented *highly relevant* to and supportive of the claimed invention. One of ordinary skill in the art would consider the evidence corroborating and convincing of the claimed invention. The PTO's view is not supported by objective evidence or by sound scientific reasoning.

Furthermore, in maintaining the enablement rejection despite applicants' submissions, the PTO has not fully and properly considered the evidence *as a whole*. Rather, the PTO appears to have reviewed each of the individual pieces of evidence that applicants have presented in isolation from the other pieces of evidence presented. Finding each individual piece lacking, the PTO has rejected the claims, without regard to what the *totality* of the evidence would indicate to one of ordinary skill in the art.

Applicants respectfully request that the PTO reconsider *as a whole* the evidence already presented in applicants' response filed April 30, 2007. Moreover, the prior evidence should also be

[1] Exhibit A also summarizes new evidence supplied with this response and labeled as Exhibits B-J.

considered with the new evidence presented with this response, *i.e.,* Exhibits B-J. Exhibits B-J constitute still further evidence of enablement in the form of additional publications which relate to immunotherapy of mesothelin-expressing tumors (including pancreatic cancer). All the evidence of record, properly considered as a whole, demonstrates that the full scope of the claimed invention is enabled.

A. The specification and the evidence presented in applicants' response filed April 30, 2007 demonstrate enablement of the full scope of the claimed invention.

1. WF-3 animal model system and in vitro experiments with WF-3 tumor cells

The PTO negates the relevance of the WF-3 model data presented in the specification based on alleged inadequacies with the particular model system used and on alleged inconsistency of the applicants' interpretation of the data. Office Action at pages 3-4.

Although a *perfect* model system for pancreatic cancer may not yet be available in the art[2], those skilled in the art recognize that experiments done using model systems such as WF-3 are highly relevant to the immunotherapy of mesothelin-expressing tumors, such as ovarian cancer and pancreatic cancer. The WF-3 cell line was developed by transforming primary peritoneal cells from C57BL/6 mice with the HPV-16 E6 and E7 oncogenes and the activated human c-Ha-*ras* gene. This transformation resulted in a tumorigenic cell line that overexpresses endogenous mesothelin, a characteristic shared with intraperitoneal tumors, such as malignant mesothelioma, ovarian cancer, and pancreatic cancer. Morphologically, WF-3 tumor cells share a number of features commonly seen in intraperitoneal tumors such as mesothelioma and ovarian tumors. Cheng et al. state, "The mesothelin-expressing WF-3 tumor model also serves as a suitable preclinical model for developing mesothelin-specific cancer immunotherapy. It is now clear that the majority of ovarian cancer, malignant mesothelioma, and pancreatic cancer express high levels of mesothelin....Because advanced-stage ovarian cancer, mesothelioma, and pancreatic cancer represent very serious illness...the development of cancer immunotherapy represents a plausible alternative approach to

control such dreadful diseases." Cheng et al., "Generation and Characterization of an Ascitogenic Mesothelin-Expressing Tumor Model," Cancer, 110:420-431 at 430 (2007; citations omitted) (Exhibit B).

The Patent and Trademark Office asserts that applicants' own interpretations of the results of immunotherapy with the mesothelin-encoding DNA vaccine in the WF-3 animal model are inconsistent. Office Action at page 4, lines 3-13. The PTO extracts a quote from applicants' April 30, 2007 response and removes it from its context. The extracted quote reads: "Induction of mesothelin-specific cytotoxic T lymphocytes is not specifically shown in this model." Office Action at page 4, lines 4-5. In context, "this model" refers to a mouse model, *i.e.,* the *in vivo* WF-3 animal model system. This statement is allegedly inconsistent with Dr. Jaffee's statement: "the DNA vaccine was shown to be capable of inducing mesothelin-specific T-cell mediated specific lysis of WF-3 cells (Example 12 and Figure 12)...." Declaration Under Rule 132 at paragraph 19.

The experiments described in Example 12 and Figure 12 of the specification relate to *in vitro* experiments involving WF-3 cells as target cells for immunized patients' T cells. In this model, mesothelin-specific T lymphocytes were demonstrated. Thus, the statement of the response and the declaration are not inconsistent because they refer to different experiments with different models systems.

The data involving *in vivo* animal models with WF-3 tumor cells described in the specification and the *in vitro* T-cell lysis of WF-3 cells described in the declaration demonstrate the enablement of the claimed invention. This evidence must be considered in combination with all the other evidence that has been presented, rather than considering each piece of evidence in isolation.

2. In vivo studies involving Listeria

Similarly, the PTO dismisses the relevance of the evidence presented in the response filed April 30, 2007 that relates to *in vivo* experiments involving the use of Listeria-based

[2] Indeed, there are no perfect models systems for any human disease. Clinical trials are always required before

immunotherapies. In particular, with respect to US 2005/0249748 (Exhibit 5 of April 30, 2007 response), the PTO states, "no where…is it shown that a) a xenogenic human pancreatic carcinoma in a mouse model has been tested, b) that the bacterium would induce an epitope specific CTL response in a pancreatic cancer model, c) the composition comprising both a polynucleotide encoding mesothelin and recombinant mesothelin-expressing Listeria monocytogenes would be effective, d) the composition induces tumor regression and e) the composition keeps the mouse tumor free after removal of the tumor." Office Action at page 5, lines 12-18. The PTO also asserts that the model used in the experiments described in the SPORE poster (Exhibit 6 of April 30, 2007 response), is not "on point" with the claimed methods. Dismissing all animal studies as irrelevant, the PTO seems to require clinical studies in order for evidence to be considered relevant. [3]

Again, the PTO has failed to consider the evidence as a whole and has failed to give proper weight to the experimental evidence. The experimental protocols used to generate evidence need not correspond exactly to the claimed methods to be relevant. Moreover, successful clinical trials are certainly not required for patentability. *In re Brana,* 34 U.S.P.Q.2d 1436 at 1441-1442 (Fed. Cir. 1995). The studies involving mesothelin-expressing *Listeria* do provide substantial support for the efficacy of the claimed invention. The PTO has provided no objective evidence which indicates, that the presented experiments are not pertinent to the claimed methods.

The PTO objects to the WF-3 mouse model because WF-3 cells implanted in the mouse are not human pancreatic cells. Office Action at page 3, line 19. The present invention is an immunotherapy. Those of skill in the art of immunology recognize that a xenograft (a human cell) cannot be used as a tumor model in an immune competent animal, including mouse, to test whether a particular agent can stimulate an epitope-specific CTL response (so-called "active" immunotherapy) that subsequently targets the tumor, resulting in its regression. Due to histo-incompatibility, human tumor cells are rejected by the adaptive cellular immune response when

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widespread human use is authorized by the FDA.

[3] The PTO should not be mandating the type of experiments that need to be performed. See (a)-(e) above. The PTO must weigh the record evidence. Failure to perform certain experiments the PTO might believe probative is simply not part of a proper weighing. No adverse inference should be drawn from applicants failure to perform experiments that the PTO might design.

injected into immune competent mice. Although xenograft cell lines can form tumors in immune incompetent mice, such as nude mice, which cannot develop cellular immunity, in such immune incompetent mice, it is impossible to test whether epitope-specific CTL targeted to the xenograft tumor can be induced. Thus, xenograft models cannot be utilized for evaluation of potential active immunotherapies. Instead, appropriate models such as the WF-3 tumor cell line have been developed for growth in corresponding syngeneic mice (C57BL/6 for the WF-3 cells). I such models studies can be conducted to test induction of epitope-specific CTL and tumor regression.

The PTO also asserts that an epitope-specific CTL response in a pancreatic cancer model has not been shown. Mesothelin-specific CTL responses have, however, been shown in more than one type of mesothelin-expressing tumor model. See the summary in Exhibit A of the experimental data in Exhibits 5 and 6. The PTO asserts that the evidence does not show that a composition comprising both a polynucleotide encoding mesothelin and recombinant mesothelin-expressing Listeria moncytogenes would be effective. Office Action at page 5, lines 16-17. In fact, the recombinant mesothelin-expressing *Listeria* described in US2005/0249748 comprise a polynucleotide that encodes a mesothelin-derived polypeptide. The record evidence shows that mesothelin-expressing *Listeria* increase survival and reduce tumor volume in mice bearing mesothelin-expressing tumors. See the summary in Exhibit A of the experimental data in Exhibits 5 and 6.

The PTO questions the safety of bacteria-based immunotherapies generally. One skilled in the art, however, would recognize which that some forms of bacteria would be suitable for administration to humans and some would not. Therefore no *undue* experimentation would be required by one of ordinary skill in the art to practice the invention.[4] Notably, the mesothelin-expressing, Listeria-based immunotherapeutic disclosed in previously presented Exhibit 6 is now the subject of an F.D.A.-approved Phase I clinical trial that is currently recruiting patients who have malignant epithelial mesothelioma, adenocarcinoma of the pancreas, non-small cell lung carcinoma, and adenocarcinoma of the ovaries. See Exhibit C. Permission by the F.D.A. to evaluate an investigational agent in humans requires demonstration of safety in rigorous toxicology studies.

Furthermore, immunotherapy platforms based on intracellular bacteria, such as *Listeria*, have received strong interest in the field, as mentioned in numerous recent publications. See, e.g., Exhibits K-N.

The data involving Listeria-based immunotherapies demonstrates the enablement of the claimed invention and must be considered in combination with all the other evidence that has been presented, *i.e.,* as a whole, and not in isolation.

3. Phase I and II clinical trials

The PTO asserts that the Phase I clinical trial data that have been presented, are not relevant to the claimed methods. "Notably, the whole tumor vaccine does not in any way resemble the inventive reagent(s) of the instant claims." Office Action at page 7, lines 1-2. The PTO likewise summarily dismisses the data from the Phase II clinical trial: "None of the clinical trials methods resemble the instant polynucleotide reagents for performing the method MHC Class binding and epitope-specific CTL induction." Office Action at page 7, lines 20-22. Again, the PTO has taken a constricted view of the data. The data present powerful evidence to those of skill in the art—even though it is not a direct test of the claimed method. The PTO's dismissal of all experimental models would lead to the result that clinical trials are necessary to provide enablement. This, however, is not the law.

The demonstrated correlation of the induction of mesothelin-specific CTL responses following immunization with an allogeneic GM-CSF-secreting tumor cell vaccine composition that overexpresses mesothelin with (a) positive clinical outcomes[5] and (b) a marker of cancer burden in pancreatic cancer patients that have been treated with an immunotherapeutic composition that overexpresses mesothelin[6] is highly relevant to and supportive of the claimed invention.

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[4] New claim 121 recites attenuated *Listeria monocytogenes*.
[5] Specification, examples 1-3
[6] Declaration under rule 132 of Elizabeth Jaffee

A recent review article by Hassan et al. reviews some of the experiments and approaches listed in Exhibit A, including some of the experiments reported in the specification of the present application. "Mesothelin targeted cancer immunotherapy," *European Journal of Cancer 44:*46-53 (2008) (Exhibit D). Hassan et al. concludes:

> The utility of mesothelin as a tumour vaccine came from a clinical trial conducted by Jaffe [*sic*] and colleagues that involved vaccination of pancreatic cancer patients with GM-CSF transduced pancreatic cancer cell lines. Out of the 14 patients treated on this study 3 developed a postvaccination delayed-type hypersensitivity (DTH) response to the autologous tumour, that was associated with prolonged survival. Subsequent immunologic studies showed that a strong and consistent induction of CD8+ T cell response to multiple HLA-A2, -A3, and –A24-restricted mesothelin epitopes occurred exclusively in the three patients who had developed a vaccine induced DTH response. ...These studies support the potential utility of mesothelin in peptide and/or vector-mediated immunotherapy protocols for the treatment of cancers that highly express mesothelin.

Hassan et al., page 51; citations omitted.

Those of ordinary skill in the art clearly consider the clinical trial data previously presented to be relevant to and supportive of mesothelin vector-mediated immunotherapy protocols, *i.e.,* the claimed invention. These data must be considered in their totality with all the other evidence that has been presented.

B. Further evidence of the enablement of the full scope of the claimed invention is found in the art.

Published references presented as Exhibits E-J accompanying this response further support the claimed invention, Applicants direct the Patent and Trademark Office's attention to the. Each of these additional references provides further experimental evidence of the ability of mesothelin to induce anti-tumor, mesothelin-specific, T-cell responses and/or of the utility of mesothelin-based

immunotherapies for treating mesothelin-expressing tumors. Relevant experiments reported in these additional references are summarized in Exhibit A. The experiments reported in these references utilize a variety of different model systems and a variety of different forms of mesothelin-based vaccines. The success and consistency in these various model systems is strong evidence of utility and enablement.

The experimental data reported in the published references presented as Exhibits E-J include experiments that utilized pancreatic tumor cells in an *in vivo* animal model. In particular, Li et al., "Mesothelin: A Malignant Factor and a Novel Therapeutic Vaccine Target for Pancreatic Cancer," Journal of Surgical Research, 137:194 (2007), reports that immunization of mice with a chimeric virus-like particle (VLP) containing mesothelin incorporated at the surface of the particle caused significant regression of preexisting pancreatic tumors and prolonged survival. In addition, elevated levels of mesothelin-specific $CD8^+$ T cell responses were observed in the vaccinated mice. See Exhibit I.

C. Taken as a whole, the substantial and varied evidence of record indicates that the full scope of the claims is enabled

In summary, a large amount of record evidence supports the full breadth of the claimed invention. The evidence is provided in the specification, in the declaration of inventor Elizabeth Jaffee, in inventor publications, and in third party publications. Taken in its totality, the evidence presented demonstrates enablement of immunotherapy of mesothelin-expressing cancers, including pancreatic cancer, the elected species. The body of evidence presented employs (a) a number of different mesothelin-expressing tumor model systems, including pancreatic and ovarian cancer cells, and (b) human clinical trial data. Furthermore, the evidence presented employs a number of different immunotherapeutic compositions, each of which comprises a polynucleotide encoding mesothelin or a portion thereof. Taken *as a whole,* the evidence demonstrates that mesothelin-encoding immunotherapeutic compositions can induce a mesothelin-specific T cell response, reduce

tumor load, inhibit tumor growth, and/or increase survival *in vivo*. The PTO has proffered no evidence to the contrary. The weight of the evidence clearly supports the enablement of the claimed invention.

In light of the record evidence, Applicants respectfully request that the rejection of the claims be withdrawn.

CONCLUSION

Each of the pending claims in this application is in condition for immediate allowance. Accordingly, we respectfully request that the PTO withdraw the outstanding rejection of the claims and allow this application to issue. If a telephone conference would expedite the prosecution of this application, we request a telephone interview.

In the event the U.S. Patent and Trademark Office determines that any additional extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 19-0733.** However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: January 18, 2008

Respectfully submitted,

By: _____

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Exhibits:

A: Summary of Selected Data Related to Mesothelin-Targeted Cancer Immunotherapy

B: Cheng et al., "Generation and Characterization of an Ascitogenic Mesothelin-Expressing Tumor Model," Cancer, 110:420-431 (2007)

C: "Study of Safety and Tolerability of Intravenous CRS-207 in Adults With Selected Advanced Solid Tumors Who Have Failed or Who Are Not Candidates for Standard Treatment," at http://www.clinicaltrials.gov, last visited 1/13/08.

D: Hassan et al., "Mesothelin targeted cancer immunotherapy," European Journal of Cancer 44:46-53 (2008)

E: Hung et al., "A DNA vaccine encoding a single-chain trimer of HLA-A2 linked to human mesothelin peptide generates anti-tumor effects against human mesothelin-expressing tumors," Vaccine 25:127-135 (2007)

F: Hung et al., "Control of mesothelin-expressing ovarian cancer using adoptive transfer of mesothelin peptide-specific CD8+ T cells," Gene Therapy14:921-929 (2007)

G: Chang et al. "Control of human mesothelin-expressing tumors by DNA vaccine," Gene Therapy, 14:1189-1198 (2007).

H: Dubensky et al., "Development of Live-Attenuated L. Monocytogenes Platforms for Immunotherapy in Patients With Carcinoma," J. Immunother., 29:647 (2006)

I: Li et al., "Mesothelin: A Malignant Factor and a Novel Therapeutic Vaccine Target for Pancreatic Cancer," Journal of Surgical Research, 137:194 (2007)

J: Yokokawa et al., "Identification of Novel Human CTL Epitopes and Their Agonist Epitopes of Mesothelin," Clin. Cancer Res. 11: 6342-6351 (2005).

K: Blattman et al., "Cancer Immunotherapy: A treatment for the masses," Science 305: 200-205 (2004)

L: Bruhn et al., "*Listeria* as a vaccine vector," Microbes and Infection, (2007) doi:10.1016/j.micinf.2007.05.010

M: Daudel et al, "Use of attenuated bacteria as delivery vectors for DNA vaccines," Expert Rev. Vaccines 6:97-110 (2007)

N: Pardoll, D., "Spinning molecular immunology into successful immunotherapy,"2:227-238 (2002)